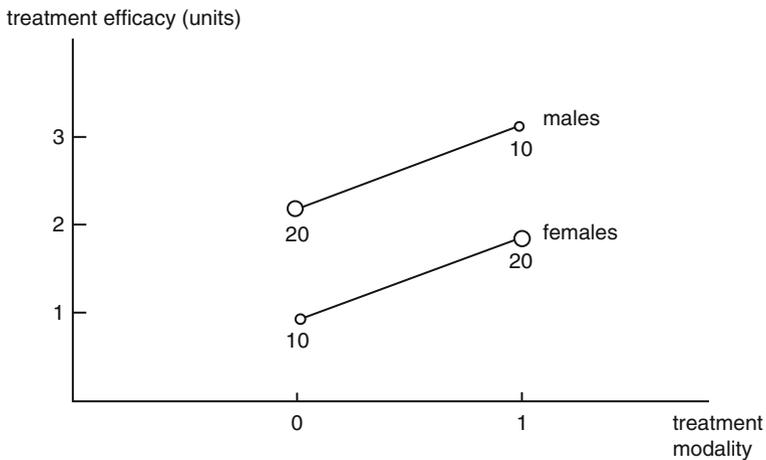# Chapter 23
Confounding

1 General Purpose

In the above study the treatment effects are better in the males than they are in the females. This difference in efficacy does not influence the overall assessment as long as the numbers of males and females in the treatment comparison are equally distributed. If, however, many females received the new treatment, and many males received the control treatment, a peculiar effect on the overall data analysis is observed as demonstrated by the difference in magnitudes of the circles in the above figure: the overall regression line will become close to horizontal, giving rise to the erroneous conclusion that no difference in efficacy exists between treatment and control. This phenomenon is called confounding, and may have a profound effect on the outcome of the study. This chapter shows how to assess confounded studies with continuous outcome data. Confounded studies with binary outcome data are reviewed in the Chap. 40.

2   Schematic Overview of Type of Data File

Outcome	Predictor (treatment modality)
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.	.

3   Primary Scientific Question

How can confounded studies be assessed.

4   Confounding Assessed with Subclassification

Confounding can be assessed by the method of subclassification. In the above example an overall mean difference between the two treatment modalities is calculated.

For treatment zero

Mean effect $\pm$ standard error (SE) $= 1.5$ units ± 0.5 units

For treatment one

Mean effect $\pm$ SE $= 2.5$ units ± 0.6 units

The mean difference of the two treatments

$$= 1.0 \text{ units} \pm \text{pooled standard error}$$
$$= 1.0 \pm \sqrt{(0.5^2 + 0.6^2)}$$
$$= 1.0 \pm 0.61$$

The t-value as calculated $= 1.0 / 0.61 = 1.639$

With 100-2 (100 patients, 2 groups) = 98 degrees of freedom the p-value of difference is calculated.

df	One-Tail = .4 Two-Tail = .8	.25 .5	.1 .2	.05 .1	.025 .05	.01 .02	.005 .01	.0025 .005	.001 .002	.0005 .001
1	0.325	1.000	3.078	6.314	12.706	31.821	63.657	127.32	318.31	636.62
2	0.289	0.816	1.886	2.920	4.303	6.965	9.925	14.089	22.327	31.598
3	0.277	0.765	1.638	2.353	3.182	4.541	5.841	7.453	10.214	12.924
4	0.271	0.741	1.533	2.132	2.776	3.747	4.604	5.598	7.173	8.610
5	0.267	0.727	1.476	2.015	2.571	3.365	4.032	4.773	5.893	6.869
6	0.265	0.718	1.440	1.943	2.447	3.143	3.707	4.317	5.208	5.959
7	0.263	0.711	1.415	1.895	2.365	2.998	3.499	4.029	4.785	5.408
8	0.262	0.706	1.397	1.860	2.306	2.896	3.355	3.833	4.501	5.041
9	0.261	0.703	1.383	1.833	2.262	2.821	3.250	3.690	4.297	4.781
10	0.260	0.700	1.372	1.812	2.228	2.764	3.169	3.581	4.144	4.587
11	0.260	0.697	1.363	1.796	2.201	2.718	3.106	3.497	4.025	4.437
12	0.259	0.695	1.356	1.782	2.179	2.681	3.055	3.428	3.930	4.318
13	0.259	0.694	1.350	1.771	2.160	2.650	3.012	3.372	3.852	4.221
14	0.258	0.692	1.345	1.761	2.145	2.624	2.977	3.326	3.787	4.140
15	0.258	0.691	1.341	1.753	2.131	2.602	2.947	3.286	3.733	4.073
16	0.258	0.690	1.337	1.746	2.120	2.583	2.921	3.252	3.686	4.015
17	0.257	0.689	1.333	1.740	2.110	2.567	2.898	3.222	3.646	3.965
18	0.257	0.688	1.330	1.734	2.101	2.552	2.878	3.197	3.610	3.922
19	0.257	0.688	1.328	1.729	2.093	2.539	2.861	3.174	3.579	3.883
20	0.257	0.687	1.325	1.725	2.086	2.528	2.845	3.153	3.552	3.850
21	0.257	0.686	1.323	1.721	2.080	2.518	2.831	3.135	3.527	3.819
22	0.256	0.686	1.321	1.717	2.074	2.508	2.819	3.119	3.505	3.792
23	0.256	0.685	1.319	1.714	2.069	2.500	2.807	3.104	3.485	3.767
24	0.256	0.685	1.318	1.711	2.064	2.492	2.797	3.091	3.467	3.745
25	0.256	0.684	1.316	1.708	2.060	2.485	2.787	3.078	3.450	3.725
26	0.256	0.684	1.315	1.706	2.056	2.479	2.779	3.067	3.435	3.707
27	0.256	0.684	1.314	1.703	2.052	2.473	2.771	3.057	3.421	3.690
28	0.256	0.683	1.313	1.701	2.048	2.467	2.763	3.047	3.408	3.674
29	0.256	0.683	1.311	1.699	2.045	2.462	2.756	3.038	3.396	3.659
30	0.256	0.683	1.310	1.697	2.042	2.457	2.750	3.030	3.385	3.646
40	0.255	0.681	1.303	1.684	2.021	2.423	2.704	2.971	3.307	3.551
60	0.254	0.679	1.296	1.671	2.000	2.390	2.660	2.915	3.232	3.460
120	0.254	0.677	1.289	1.658	1.980	2.358	2.617	2.860	3.160	3.373
∞	0.253	0.674	1.282	1.645	1.960	2.326	2.576	2.807	3.090	3.291

The above t-table has a left-end column giving degrees of freedom (≈ sample sizes), and two top rows with p-values (areas under the curve = p - values), one-tail meaning that only one end of the curve, two-tail meaning that both ends are assessed simultaneously. The t-table is, furthermore, full of t-values, that, with ∞ degrees of freedom, are equal to z-values (Chap. 36). The t-values are to be understood as mean results of studies, but not expressed in mmol/l, kilograms, but in so-called SEM-units (Standard error of the mean units), that are obtained by dividing your mean result by its own standard error. With many degrees of freedom (large samples) the curve will be a little bit narrower, and more in agreement with nature.

We have 98 degrees of freedom, and, so, we will need the rows between 60 and 120 to estimate the area under curve of a t-value of 1.639. A t-value larger than 1.980 is required for an area under curve significantly different from zero ($=$ p-value < 0.05). Our area under the curve of 1.639 is much larger than 0.05. We cannot reject the null-hypothesis of no difference in the data here.

In order to assess the possibility of confounding, a weighted mean has to be calculated. The underneath equation is adequate for the purpose.

$$\text{Weighted mean} = \frac{\text{Difference}_{\text{males}}/\text{its SE}^2 + \text{Difference}_{\text{females}}/\text{its SE}^2}{1/\text{SE}^2_{\text{males}} + 1/\text{SE}^2_{\text{females}}}$$

For the males we find means of 2.0 and 3.0 units, for the females 1.0 and 2.0 units. The mean difference for the males and females separately are 1.0 and 1.0 as expected from the above figure. However, the pooled standard errors are different, for the males 0.4, and for the females 0.3 units.

According to the above equation a weighted t-value is calculated

$$\text{Weighted mean} = \frac{\left(1.0/0.4^2 + 1.0/0.3^2\right)}{\left(1/0.4^2 + 1/0.3^2\right)}$$
$$= 1.0$$
$$\text{Weighted SE}^2 = 1/\left(1/0.4^2 + 1/0.3^2\right)$$
$$= 0.0576$$
$$\text{Weighted SE} = 0.24$$
$$\text{t-value} = 1.0/0.24 = 4.16$$

According to the above t-table with 98 degrees of freedom a t-value of 4.16 is much larger than the critical t-value producing a $p < 0.05$. Our result is very significant: p-value $= <0.001$.

The weighted mean is equal to the unweighted mean. However, its SE is much smaller. It means that after adjustment for confounding a very significant difference is observed.

5   Conclusion

Other methods for assessing confounding include multiple regression analysis and propensity score assessments. Particularly, with more than a single confounder these two methods are unavoidable. Propensity score assessments is covered in the Chap. 32.

6 Note

More background, theoretical and mathematical information of confounding is given in Statistics applied to clinical studies 5th edition, Chap. 28, Springer Heidelberg Germany, 2012, from the same authors.